SCIENTIFIC ABSTRACT: SCH 412499 (RAD- $P21^{WAF1/CIP-1}$)

This Phase I study is planned as a single dose, dose-escalation safety trial involving the targeted gene transfer of $p21^{WAF1/Cip1}$ via an adenoviral vector as adjunctive therapy for trabeculectomy (glaucoma filtration surgery) to prevent surgical failure due to wound healing and scarring of the surgical site. Up to 18 subjects with uncontrolled glaucoma in whom trabeculectomy is indicated will be enrolled. Subjects will receive SCH 412499 in 3 dose cohorts, by subconjunctival injection one day prior to the scheduled trabeculectomy.

Glaucoma is an optic neuropathy characterized by elevation of intra-ocular pressure (IOP) resulting in the degeneration of the optic disc and loss of vision. The majority of medical and surgical strategies to treat glaucoma are directed at lowering IOP. Trabeculectomy reduces IOP through a procedure that creates a hole (fistula) under the conjunctiva and through the sclera into the anterior chamber and allows for drainage of aqueous humor into the subconjunctival space. Surgical failure results from the proliferation and activation of ocular fibroblasts and consequent scarring of the subconjunctival space, thus restricting or blocking the outflow of aqueous humor, with a concomitant rise in IOP. The success rate of trabeculectomy surgery has been enhanced by the adjunctive use of anti-proliferative agents including 5-fluorouracil (5-FU) and mitomycin C (MMC); however both of these drugs have significant side effects associated with their use and 5-FU must be applied using multiple subconjunctival injections that frequently cause discomfort to the patient.

$p21^{WAF1/Cip1}$ is a nuclear protein that negatively regulates the cell cycle by inhibiting the G1 to S phase transition. Preclinical experiments in ocular fibroblasts have demonstrated exogenous expression of p21 protein, and, dose-dependent, gene-specific inhibition of proliferation *in vitro* after treatment with SCH 412499. Studies in rabbit models of glaucoma surgery have demonstrated adenovirus-mediated transgene expression in target cells *in vivo* (conjunctival fibroblasts) and p21 mRNA expression up to 2 months post administration. The prolonged duration of expression following a single administration of SCH 412499 corresponds with the

interval of aggressive wound healing after surgery. Reduced fibroproliferation and inhibition of wound healing have been demonstrated after a single subconjunctival injection of SCH 412499 in this rabbit model. Local application of SCH 412499 in a primate disease model resulted in p21-specific maintenance of IOP reduction following trabeculectomy. Quantitative reduction of IOP is proposed as the primary response variable for future therapeutic clinical trials with SCH 412499. The first proposed clinical study is intended to evaluate the safety and tolerability of SCH 412499. Non-clinical safety evaluations in non-human primates have been completed and support the initiation of human trials. Based on these data, we propose to use anti-proliferative gene therapy to inhibit post surgical wound healing and scarring as a means to prevent trabeculectomy failure.